

N<sup>o</sup> 18,825



A.D. 1904

Date of Application, 31st Aug., 1904

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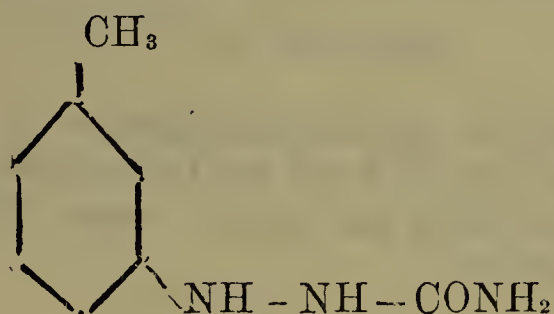
[Communicated by the FARBENFABRIKEN VORMALS FRIEDRICH BAYER & Co., of Elberfeld in the Empire of Germany.]

PROVISIONAL SPECIFICATION.

“Improvements in the Manufacture and Production of a Pharmaceutical Compound.”

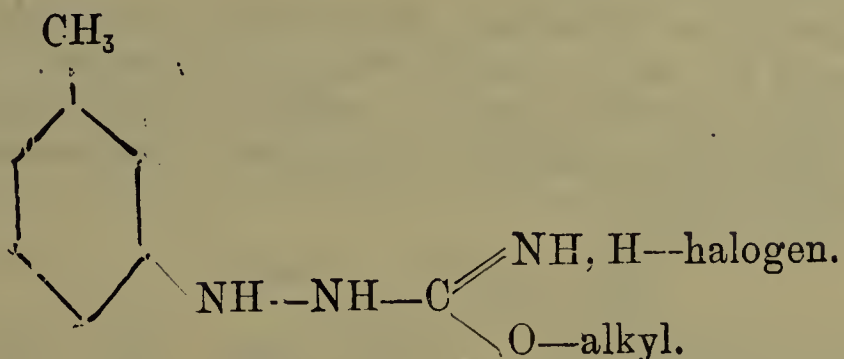
I, HENRY EDWARD NEWTON of the Office for Patents 6 Breems Buildings, Chancery Lane, in the County of London, Patent Agent. do hereby declare the nature of this invention to be as follows:—

My foreign correspondents discovered some time since that the meta-tolylsemi-  
5 carbazide having the formula :



possesses valuable therapeutic, especially antipyretic, properties, and that this new compound can be obtained *e.g.* by treating meta-tolylhydrazine ( $\text{CH}_3-\text{C}_6\text{H}_4-\text{NH}-\text{NH}_2$ ), or salts thereof, with derivatives of carbonic acid such as urea,  
10 urethanes, cyanic acid, or the like by the employment of which the group— $\text{CO}-\text{NH}_2$  can be introduced into the hydrazine molecule.

My foreign correspondents have now found that the meta-tolylsemicarbazide of the above given formula can also be obtained on splitting off one molecule of  
15 halogen alkyl from the hitherto unknown salts of the imidoethers of the metatolylhydrazine carboxylic acid having the formula :

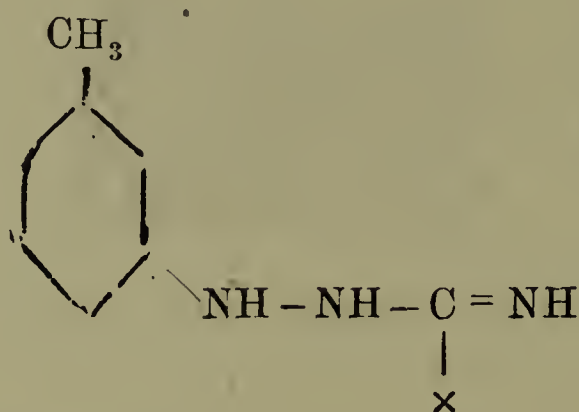


by heating these bodies to higher temperatures or on transforming these salts into the metatolylsemicarbazide by treatment with water, or on treating the hitherto

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unknown halogenimides or the amidine of metatolyldiazine carboxylic acid of the following general formula :



(X meaning halogen or the amidogroup) with water or with agents capable of splitting off ammonia. 5

The metatolylsemicarbazide can also be obtained by reducing the hitherto unknown metatolylazocarbonamide having the formula :



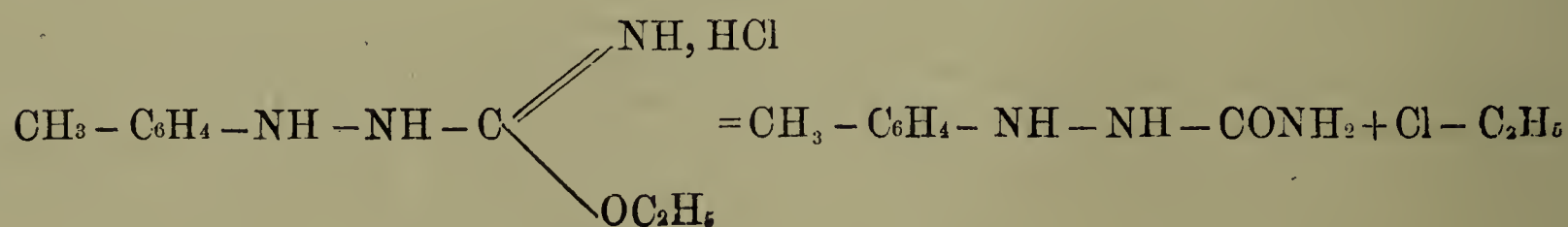
which can be obtained by treating the ester of metatolylazocarboxylic acid with ammonia. 10

The hydrochlorides of the imidoethers of metatolylhydrazine carboxylic acid, for instance, can be obtained by the combination of an alcohol with the nitrile of metatolylhydrazine carboxylic acid in an ethereal solution under the influence of hydrochloric acid gas. The nitrile of meta-tolylhydrazine carboxylic acid can be obtained by the action of cyanogen bromide on meta-tolylhydrazine. 15

In order to illustrate the process more fully the following examples are given, the parts being by weight.

## EXAMPLE A.

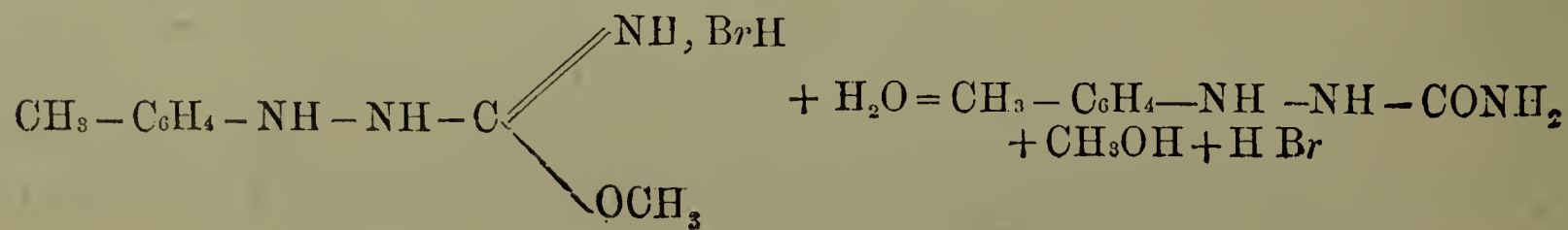
100 parts of the hydrochloride of the ethylimidoether of the meta-tolylhydrazine carboxylic acid are heated in an oil bath to 130—140° Centigrade until ethyl chloride is no longer disengaged from the molten mass. The reaction takes place according to the following equation : 20



On recrystallizing the cold mass from water the metatolylsemicarbazide is obtained in a pure state melting at 183—184° Centigrade. 25

## EXAMPLE B.

50 parts of the hydrogen bromide salt of the methylimidoether of meta-tolylhydrazine-carboxylic acid are mixed with 200 parts of water. At first a clear solution results but after a short while the solution gets troubled. It is then heated until a clear solution is obtained once more. The reaction takes place according to the following equation : 30





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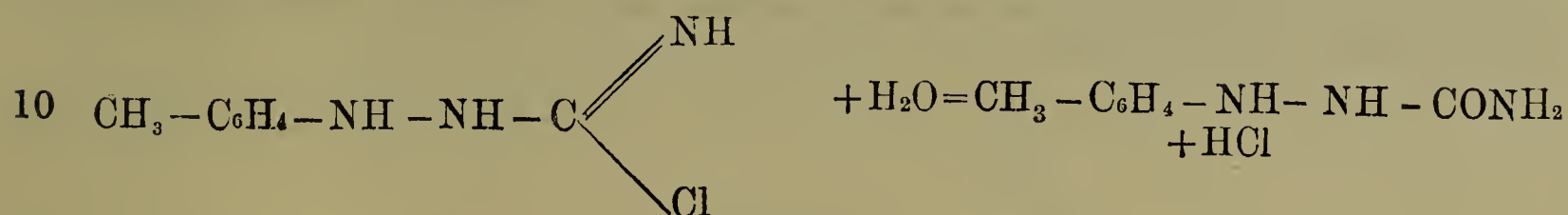
The metatolylsemicarbazide thus obtained deposits on cooling. It is filtered off and purified by a recrystallization from water.

The process proceeds in an analogous manner on using salts of other imidoethers of the meta-tolylhydrazine carboxylic acid.

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## EXAMPLE C.

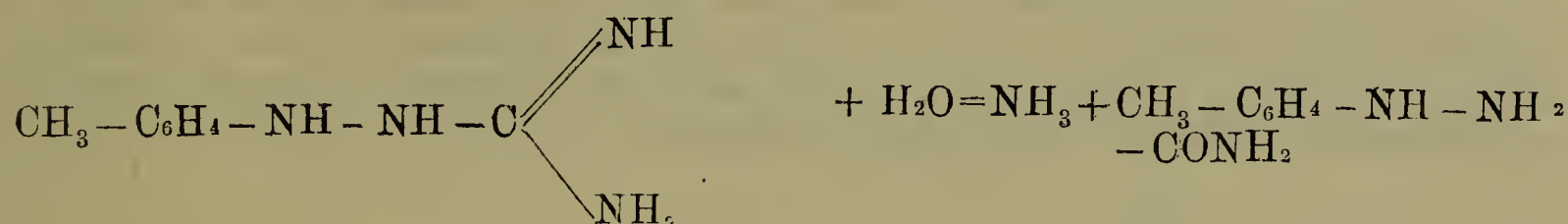
One part of the imido chloride of metatolylhydrazine carboxylic acid (obtainable by the action of hydrochloric acid gas on the nitrile of the metatolylhydrazine carboxylic acid dissolved in ether) is mixed with 25 parts of water. On heating, the reaction takes place according to the following equation :



The metatolylsemicarbazide thus precipitated is filtered off and recrystallized from water.

## EXAMPLE D.

15 A mixture of 20 parts of a 20 *per cent* solution of barium hydroxide, 50 parts of water and 10 parts of the hydrochloride of the amidine of metatolylhydrazine carboxylic acid is heated to 120° for several hours. The reaction takes place according to the following equation :



20 The metatolylsemicarbazide thus obtained is filtered off and recrystallized from water.

## EXAMPLE E.

25 A mixture of 10 parts of metatolylazocarbonamide (M.Pt. 72—74° orange-red crystals) 200 parts of water, 5 parts of acetic acid and 5 parts of zinc dust is heated until the mass becomes uncolored. The metatolylsemicarbazide thus obtained is then filtered off and recrystallized from water.

The hydrochloride of the amidine of metatolylhydrazine carboxylic acid mentioned in Example D can be prepared on heating an alcoholic solution of cyanamide with the hydrochloride of metatolylhydrazine.

30 My foreign correspondents do not intend to confine themselves to the particulars given in the above examples which are merely typical and can be varied within wide limits without altering thereby the nature of the above invention.

Dated this 31st day of August, 1904.

NEWTON & SON  
6 Breems Buildings, Chancery Lane, London, E.C.  
Agents for the Applicant.

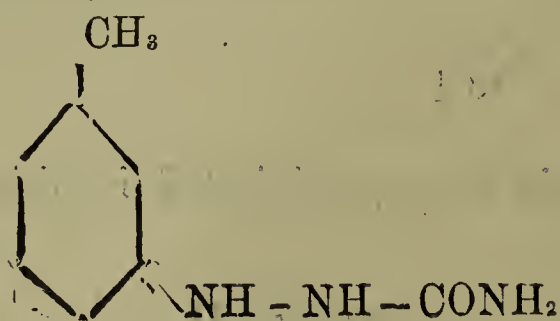
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## COMPLETE SPECIFICATION.

**“Improvements in the Manufacture and Production of a Pharmaceutical Compound.”**

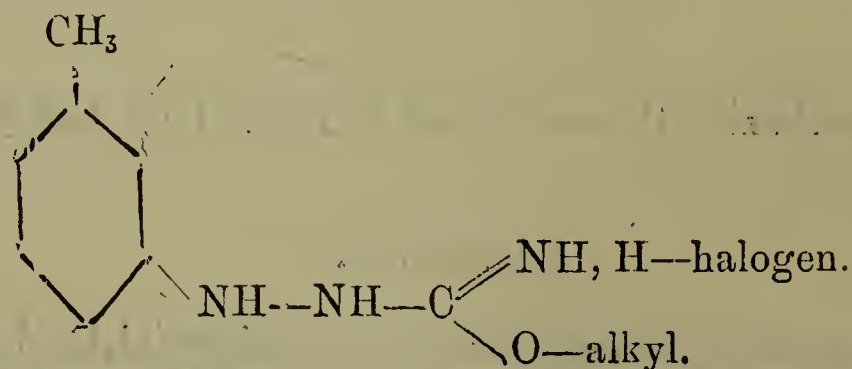
I, HENRY EDWARD NEWTON, of the Office for Patents, 6 Breems Buildings, Chancery Lane, in the County of London, Patent Agent, do hereby declare the nature of this invention and in what manner the same is to be performed, to be particularly described and ascertained in and by the following statement:—

My foreign correspondents discovered some time since, that the meta-tolylsemi- 5 carbazide having the formula :

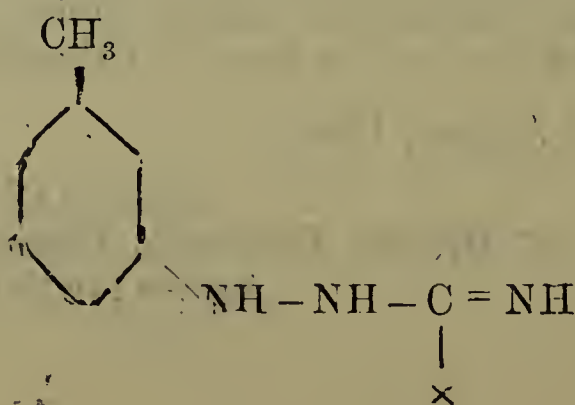


possesses valuable therapeutic, especially antipyretic, properties and that this new compound can be obtained *e.g.* by treating meta-tolylhydrazine ( $\text{CH}_3 - \text{C}_6\text{H}_4 - \text{NH} - \text{NH}_2$ ) or salts thereof, with such derivatives of carbonic acid, (for instance urea, 10 urethanes, cyanic acid, or the like) by the employment of which the group  $-\text{CO} - \text{NH}_2$  can be introduced into the hydrazine molecule.

My foreign correspondents have now found that the meta-tolylsemicarbazide of the above given formula can also be obtained on splitting off one molecule of 15 halogen alkyl from the hitherto unknown salts of the imido ethers of the meta-tolylhydrazine carboxylic acid having the formula :



by heating these bodies to higher temperatures or on transforming these salts into the metatolylsemicarbazide by treatment with water; or on treating with water the hitherto unknown halogenimides of metatolylhydrazine carboxylic acid or on 20 treating with agents capable of splitting off ammonia the amidine of this acid, which compounds have the following general formula :

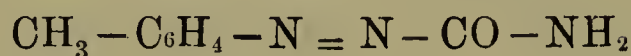




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(X meaning halogen or the amidogroup)

The metatolylsemicarbazide can also be obtained by reducing the hitherto unknown metatolylazocarbonamide having the formula :



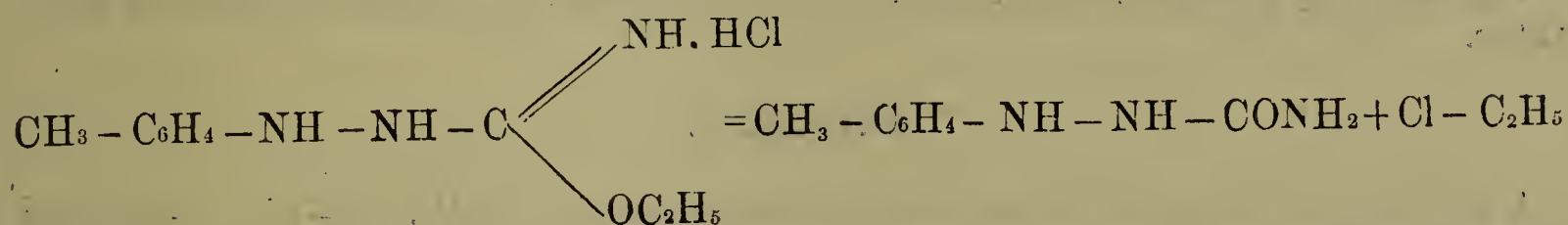
5 which can be obtained by treating the esters of metatolylazocarboxylic acid with ammonia.

The hydrochlorides of the imidoethers of metatolylhydrazine carboxylic acid, for instance, can be obtained by the combination of an alcohol with the nitrile of metatolylhydrazine carboxylic acid in an ethereal solution under the influence of hydrochloric acid gas. The nitrile of metatolylhydrazine carboxylic acid can be obtained by the action of cyanogen bromide on meta-tolylhydrazine.

In order to illustrate the process more fully the following examples are given, the parts being by weight.

EXAMPLE A.

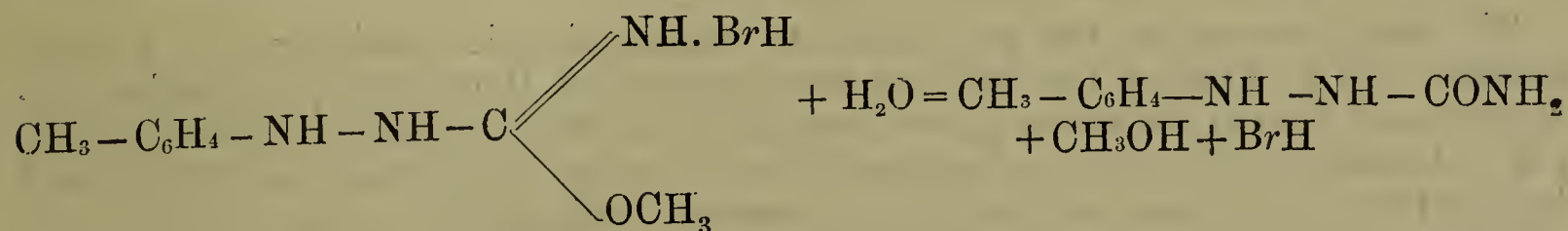
15 100 parts of the hydrochloride of the ethylimidoether of the meta-tolylhydrazine carboxylic acid are heated in an oil-bath to 130—140° Centigrade, until ethyl chloride is no longer disengaged from the molten mass. The reaction takes place according to the following equation :



20 On recrystallizing the cold mass from water the meta-tolylsemicarbazide is obtained in a pure state melting at 183—184° Centigrade.

EXAMPLE B.

50 50 parts of the hydrogen bromide salt of the methylimidoether of meta-tolylhydrazine-carboxylic acid are mixed with 200 parts of water. At first a clear solution results but after a short while the solution gets turbid. It is then heated until a clear solution is again obtained. The reaction takes place according to the following equation :



30 The metatolylsemicarbazide thus obtained deposits on cooling. It is filtered off and purified by a recrystallization from water.

The process proceeds in an analogous manner on using salts of other imidoethers of the meta-tolylhydrazine carboxylic acid.

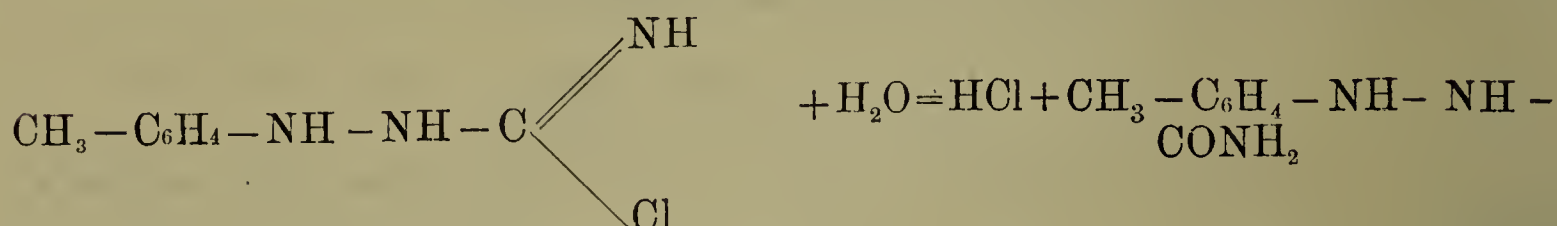
EXAMPLE C.

35 One part of the imido chloride of meta-tolylhydrazine carboxylic acid (obtainable by the action of hydrochloric acid gas on the nitrile of the metatolylhydrazine



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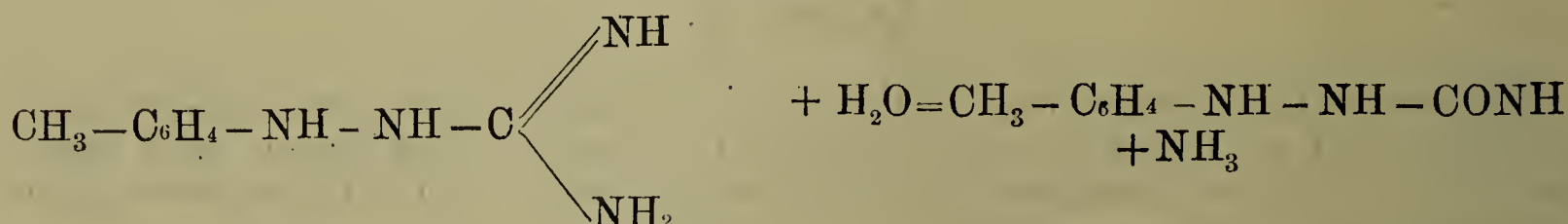
carboxylic acid dissolved in ether) is mixed with 25 parts of water. On heating, the reaction takes place according to the following equation :



The metatolylsemicarbazide thus precipitated is filtered off from the cold liquid and recrystallized from water. 5

## EXAMPLE D.

A mixture of 20 parts of a 20 *per cent.* solution of barium hydroxide, 50 parts of water and 10 parts of the hydrochloride of the amidine of metatolylhydrazine carboxylic acid is heated to 120° for several hours in a closed vessel. The reaction takes place according to the following equation : 10



The metatolylsemicarbazide thus obtained is filtered off and recrystallized from water.

## EXAMPLE E.

A mixture of 10 parts of metatolylazocarbonamide (M.Pt. 72—74° orange-red crystals), 200 parts of water, 5 parts of acetic acid and 5 parts of zinc dust is heated until the mass becomes uncolored. The metatolylsemicarbazide thus obtained is then filtered off and recrystallized from water. 15

The hydrochloride of the amidine of metatolylhydrazine carboxylic acid mentioned in Example D. can be prepared on heating an alcoholic solution of cyanamide with the hydrochloride of metatolylhydrazine. 20

My foreign correspondents do not intend to confine themselves to the particulars given in the above examples which are merely typical and can be varied within wide limits without altering thereby the nature of the above invention.

Having now particularly described and ascertained the nature of the said invention and in what manner the same is to be performed, as communicated to me from abroad, I declare that what I claim is :— 25

The new process for the production of metatolylsemicarbazide, which process consists (1) in heating the salts of imido-ethers of the metatolylhydrazine carboxylic acid having the above given formula, (2) in treating these salts with water, (3) in treating with water the halogenimides of metatolylhydrazine carboxylic acid having the above given formula, (4) in treating with agents capable of splitting off ammonia the amidine of metatolylhydrazine carboxylic acid having the above given formula or (5) in treating with reducing agents the metatolylazocarbonamide having the above given formula, substantially as hereinbefore described. 30 35

Dated this 2nd day of May, 1905.

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Agents for the Applicant.





